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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Beyond Regulation of Acid Secretion: A Novel Role for Histamine in Gastric Macrophage Differentiation and Function

Histamine is a biogenic amine that is widely recognized as a mast cell–derived inflammatory mediator that contributes to local inflammatory reactions by increasing vascular permeability. In the stomach, histamine also is a key driver of acid secretion by parietal cells, and histamine receptor antagonists, such as cimetidine or ranitidine, are commonly used as long-term treatments to inhibit parietal cell acid production in patients with acid reflux disease. Although mast cells are considered the major producers of histamine in the body, histamine secretion by multiple other cell types including neuronal cells and myeloid cells has been reported. In human gastric mucosa, enterochromaffin-like cells were found to be the major source of histamine for the regulation of parietal cell acid secretion.

To elucidate the role of histamine in gastric physiology, several previous studies used a histamine-deficient mouse, the histidine decarboxylase knockout mouse (HDC-KO), which lacks the biosynthetic enzyme required to generate histamine from the amino acid L-histidine.[1] Over the course of multiple months, the HDC-KO mice develop spontaneous hypertrophic gastropathy with dysregulated gastric epithelial cell differentiation.[2,3] Similar pathologic changes to the gastric architecture are seen in a rare human disease, Ménétrier disease,[4] making this mouse model translationally relevant. Development of hypertrophic gastropathy in the HDC-KO model was thought to be caused by histamine regulating both parietal cell acid secretion and gastric epithelial cell growth and lineage differentiation.[3] However, in an interesting new study published in this edition of *Cellular and Molecular Gastroenterology and Hepatology*, Kim et al[5] demonstrate that vastly more complex pathways and feedback loops involving the bone marrow, peripheral immune mechanisms, the gastric microbiome, and gastric epithelial cells lead to hypertrophic gastropathy upon histamine deficiency.

Kim et al[5] observed that, in addition to the morphologic and functional changes to the gastric epithelium, HDC-KO mice developed severe gastric bacterial overgrowth and inflammatory changes to the gastric mucosa with a significant long-term increase in gastric macrophages. Importantly, hyperplastic gastropathy did not occur in germ-free HDC-KO mice, indicating a central role for the gastric microbiota in the regulation of epithelial cell growth and differentiation. Based on these observations and previous studies that had shown a role for histamine in myeloid cell differentiation,[6,7] the authors focused on the role of gastric macrophages in the development of hypertrophic gastropathy and bacterial dysbiosis in HDC-KO mice.

First, single cell RNASeq analysis was used to perform an in-depth characterization of the murine gastric macrophage population, which revealed 3 major macrophage subsets: (1) F4/80^{+} CD11b^{+} IL-1β^{+} M1 macrophages, (2) F4/80^{+}CD11b^{+} CD93^{+} M2 macrophages, and (3) an F4/80^{neg} CD11b^{+} MHC-II^{+} subset with high phagocytic capacity. In functional experiments, gastric macrophages from the HDC-KO mice showed significantly decreased phagocytosis, associated with a reduced expression of complement receptors (CD21/35). Kim et al[5] then used a highly creative experimental approach to differentiate between the role of parietal cells versus macrophages in gastric dysbiosis. In the HDC-KO mice, all bacteria were eliminated using antibiotics, the stomach was acidified through drinking water, and then the HDC-KO mice were gavaged with bacteria from wild-type mice. Significant bacterial overgrowth was still present in the HDC-KO mice despite normal gastric pH, demonstrating that gastric dysbiosis in HDC-KO mice was not merely caused by reduced parietal cell acid secretion but involved a defective host response. Importantly, experiments using bone marrow chimeras demonstrated that transfer of wild-type macrophages into HDC-KO mice fully eliminated gastric inflammation and restored gastric morphology and bacterial colonization. These results confirm a role of gastric macrophages for hypertrophic gastropathy and gastric dysbiosis in HDC-KO mice and also point to the bone marrow rather than the stomach itself as a key site for histamine-dependent macrophage differentiation.

It is important to define to what extent the phagocyte defects in the HDC-KO mice impact *Helicobacter pylori* pathogenesis, given previous contradictory reports on macrophage function in murine *H pylori* infection. Whereas Viladomiu et al[8] showed that gastric CD11b^{+}F4/80^{hi}CD64^{+}CX3CR1^{+} macrophages suppress gastric inflammation but are unable to effectively control *H pylori* colonization, Schumacher et al[9] showed that CD11b^{+}F4/80^{+}Ly6C^{hi} macrophages contribute to gastric inflammation in *H pylori*–infected mice. Notably, a previous *H pylori* infection study found milder cytokine responses and reduced gastric pathology in HDC-KO mice compared with wild-type mice infected at 6 to 8 weeks of age.[10] However, most changes in the study by Kim et al[5] required 12 months to develop. Future research also is needed to determine whether hyperplastic gastropathy in human Ménétrier disease involves histamine deficiency, macrophage dysfunction, or gastric dysbiosis.

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